TR40 Sterilizing Filtration of Gases
A comparison with
TR26 Sterilizing Filtration of Liquids

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PDA Technical Report 40 Sterilizing Filtration of Gases

- Published Jan/Feb 2005
- Educational guide to complement TR26
- Committee

  F. Bing (Chair), S. Sundaram (Co-chair)
  B. Bardo, T. Britton, R. Conway, T. Feeser,
  H. Haughney, A. M. Jones, M. Jornitz, S. Langille
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  T. Meltzer, D. Meyer, G. Morris, D. Ridealgh
  H. Schroeder, P. Stinavage, A. M. Trotter
  – 7 manufacturers, 6 users, 4 consultants, 1 FDA

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Similarities

- Both technical reports are considered to be educational guides rather than mandatory or implied standards

- Both describe filter retention mechanisms, selection criteria, sterilization methods, validation of retention capabilities and integrity test methods

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Differences

- The risk associated with liquid filtration is significantly greater than the risk associated with gas filtration
  - Bioburden potential is higher in liquid
  - Example suggested action levels
    - 100 cfu mL for Purified water (liquid)
    - 100 cfu/M^3 for class 8 /100,000 cleanroom

      = 0.0001 cfu/mL (air)

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Removal mechanisms

- Gas filters have additional retention mechanisms and will retain smaller particles

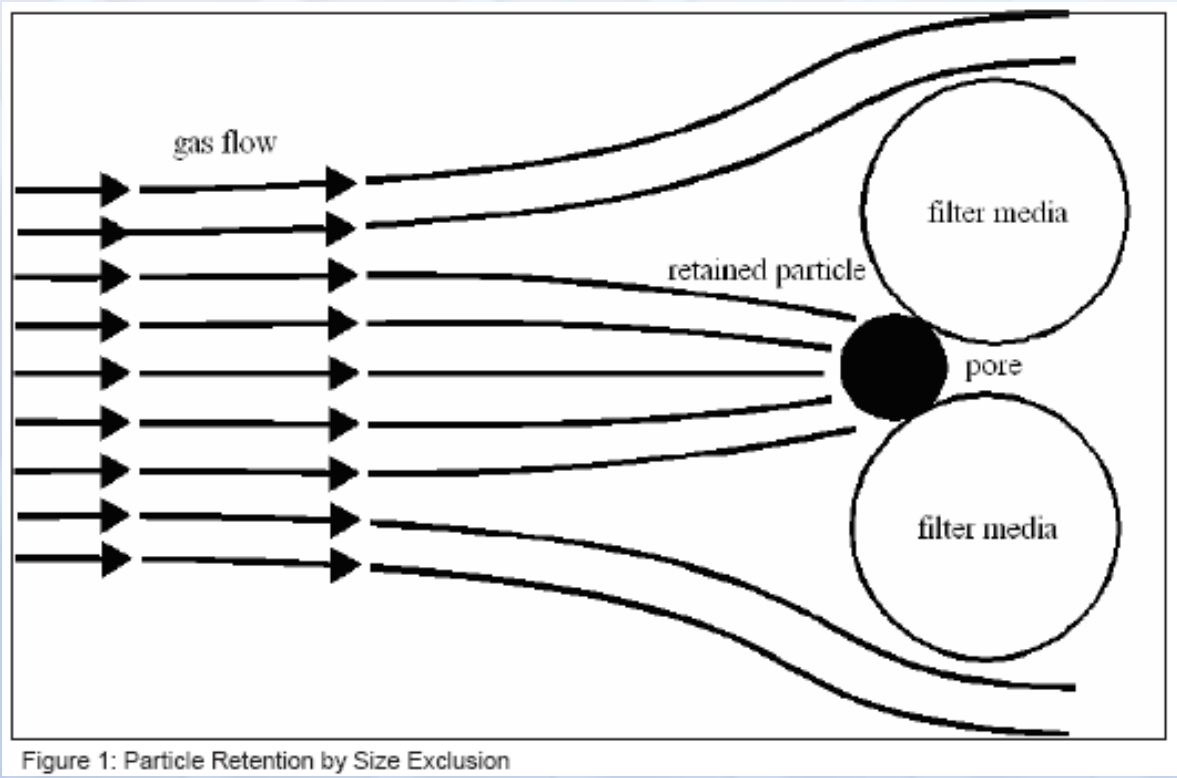

Figure 1: Particle Retention by Size Exclusion

–Size exclusion is used in both liquid and gas

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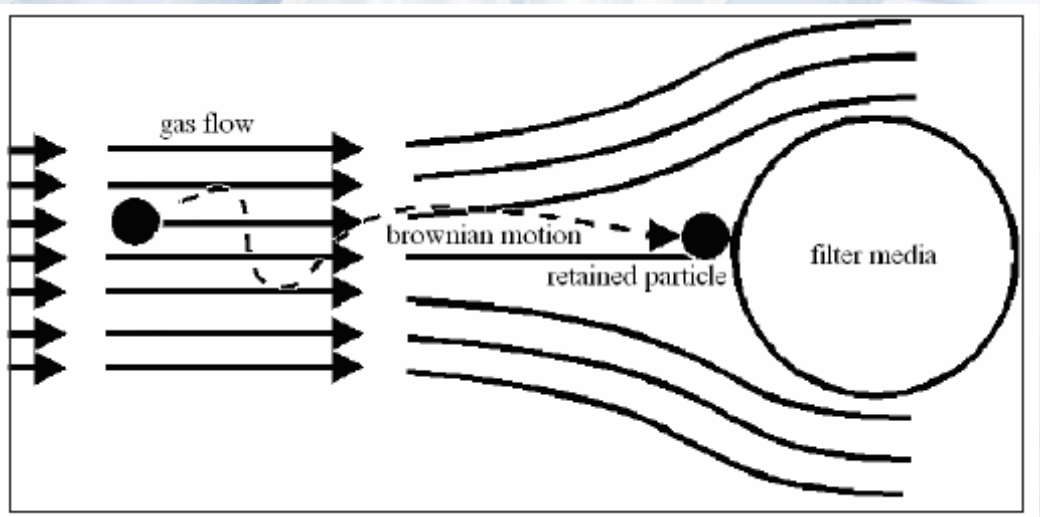

Figure 2: Diffusional Interception

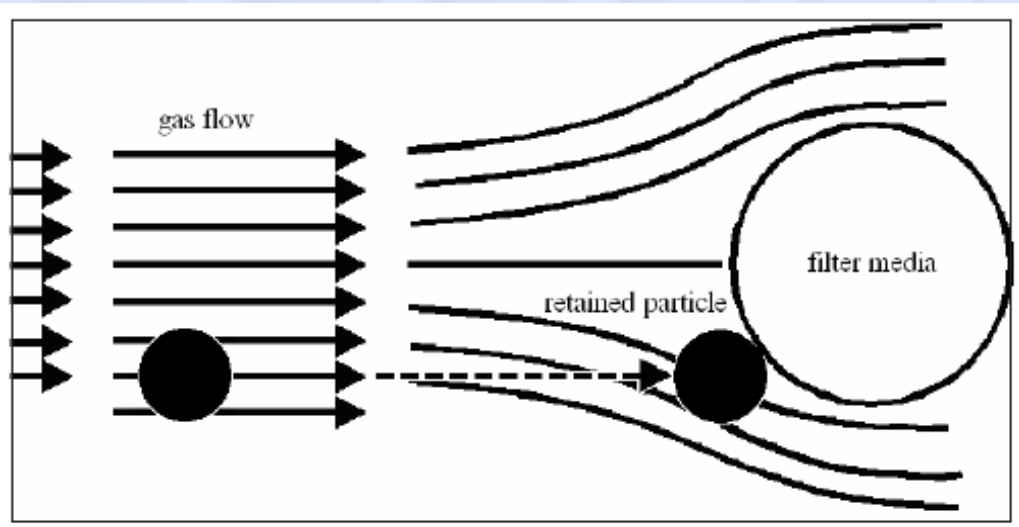

Figure 3: Inertial Impaction

- Smaller particles in gas
  - Diffusional interception
  - Electrostatic attraction
  - Inertial impaction

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Most penetrating particle size

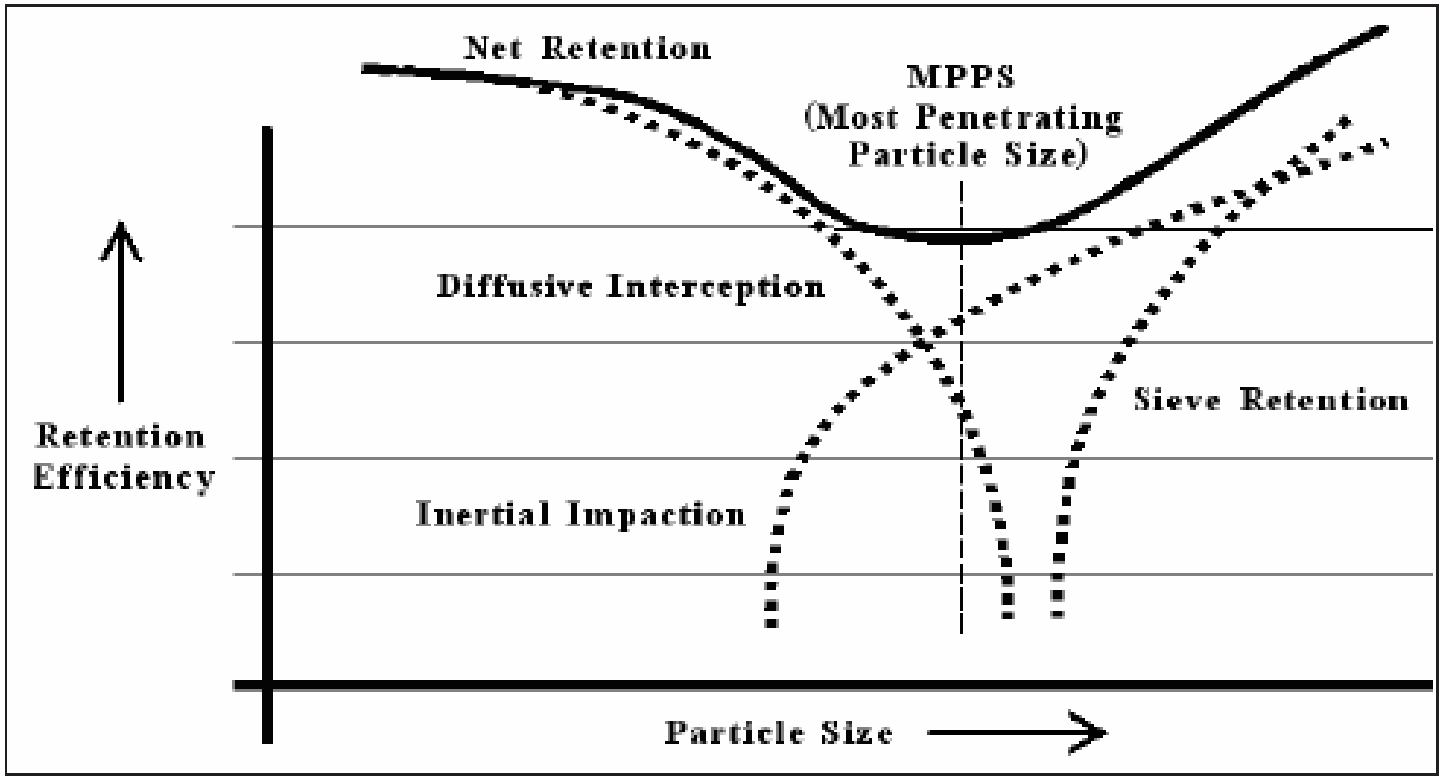

Figure 4: Effect of Various Retention Mechanisms of Particles Retained from a Gas Stream as a Function of Particle Size

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Hydrophobic membranes

- Do not readily wet with water and so avoid water blockage that can occur with hydrophilic membranes

Polymer	Critical surface tension (dynes/cm)
PTFE	18
PVDF	25
Polypropylene	29.5
Polyethylene	32

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Pore size ratings

- True pore size should not be confused with nominal pore rating given by the manufacturer
- Even less meaning in the ratings of gas than liquid filters
- Gas filters are best described by performance on a challenge test correlated to a filter integrity test
- Liquid rated “sterilizing grade” 0.2 µm are much more efficient in retention in dry gas streams

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Filter selection criteria

- Retention capacity
- Integrity testing
- Flow rate & throughput
- Materials of construction
  - Hydrophobicity
  - Durability
  - Toxicity
  - Particle shedding
  - Compatibility

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Design considerations

- Minimize water blockage
  - Orient housing to allow condensation to drain
  - Jacket or heat trace housing (3-5°C above process temperature)
  - Open vent valve
  - Coalescing prefilter
- Integrity test
  - Test considerations
  - Wetting
  - Drying (blow down)

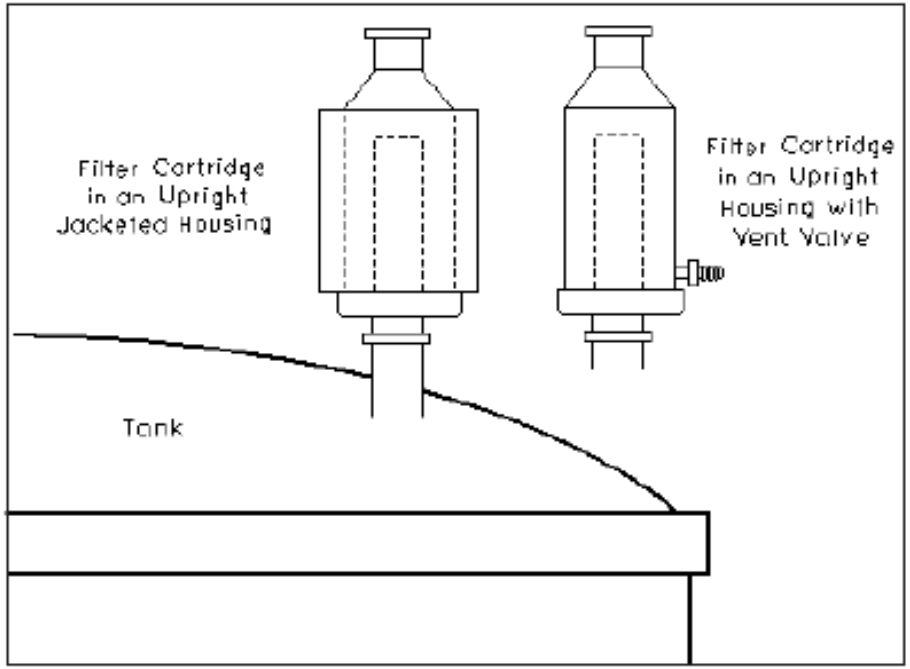

Figure 6: Examples with Filter Oriented for Drainage of Condensate with Steam Jacket or Open Lower Vent Valve

Ideal sterile gas filter

- Retains microorganisms even under adverse conditions such as high humidity
- High thermal /mechanical resistance
- Withstand multiple steam cycles
- High gas flow at low Δ P
- Hydrophobic
- Non fiber releasing
- Integrity testable – correlated to removal efficiency
- Easy to install and maintain
- Compatible with application

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Most critical applications

- Gas is in contact with sterile final product or critical surfaces of the associated equipment
  - Compressed process gases for asceptic fill operations
  - Vacuum break gases for lyophilizers and critical autoclaves
  - Headspace gases used to flush vials and ampoules
  - Sterile bulk holding tank vents
  - Nitrogen blankets
- Filter should be qualified with a liquid based bacterial challenge test and have a physical integrity test correlated to retention in liquid

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Moderately critical applications

- Filtered gas is not in direct contact with exposed sterile product or surfaces
  - Intermediate process steps
  - Air supplied to a fermentation process
- Filters qualified with aerosol based bacterial challenge, correlated to a physical integrity test, are appropriate

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Other applications

- Applications that only require a reduction in bioburden have less stringent requirements

- Because the retention expectation is similar to HEPA filters, dispersed oil aerosol challenges are deemed acceptable to establish the retention capability

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Special cases

- Some applications may have additional or more specific requirements
  - e.g. bacteriophage control or virus retention
- Different articles have been published regarding retention of contaminants bacteria, phages under different conditions
- Applicability of the data to the particular situation needs to be evaluated on a case by case basis

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Validation of retention capabilities

- No specific standard that defines the retention requirements of a membrane filter used to sterilize gases
- Several approaches
  - Liquid challenge
  - Aerosol challenge
    - bacteria, spores, virus, dispersed oil
- Retention studies do not need to be repeated by user
- Should evaluate applicability of the retention study to the application

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Liquid challenge

- Liquid bacterial challenge represents the worst-case condition since retention in liquids is lower than gases
- ASTM F838 or comparable test on discs, capsule or high area cartridge
  - *Brevundimonas diminuta* ATCC® 19146™
  - 100% of effluent must be analyzed

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Aerosol challenges

- Bacterial (spore) aerosol challenges are always less rigorous than liquid challenges even though they do represent the way the filter is challenged in a dry gas process

- Phage/viral challenges may be the least rigorous because in gas filtration, the smallest particles are not the most difficult to retain

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Aerosol bacterial challenge

- *B. diminuta* - watch conditions for viability
- *Bacillus subtilis* -spores resist drying but are larger than vegetative cells
- Nebulizer generates droplets
- Andersen Sampler can be used to assess droplet size down to 0.65 µm
- Filtered gas is analyzed using liquid impingers
- Control, without filter is run to determine the challenge level
- Lower flow rates may be worst-case scenario

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Sample aerosol challenge apparatus

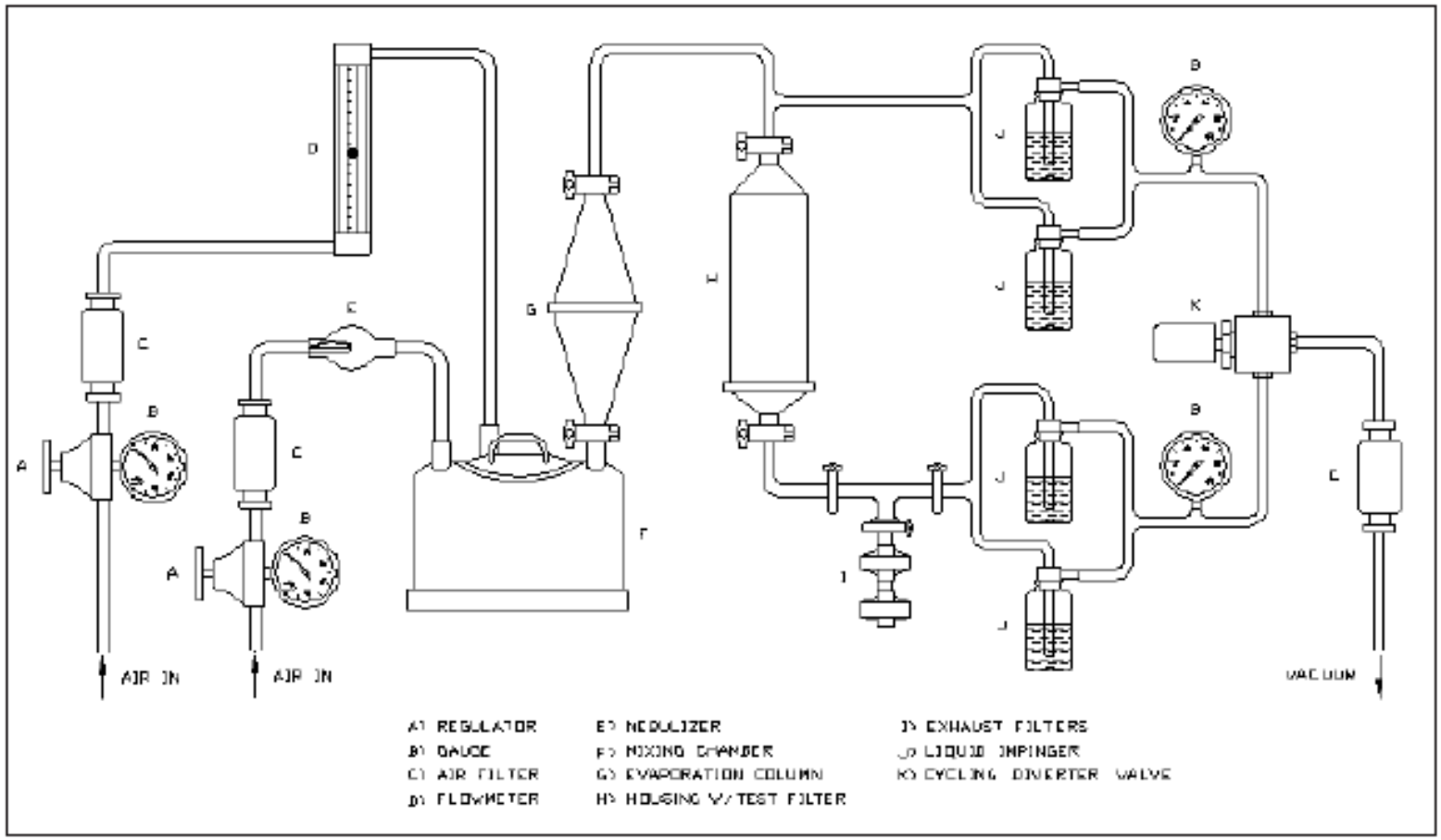

Figure 7: Schematic of Aerosol Challenge Test (Split Stream Approach)

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Viral aerosol challenges

- No standards
- Similar apparatus
- Bacteriophage: Phi X-174, PP7, MS2, T1
- Virus sizes = 25 nm to 180 nm
- Andersen Sampler can demonstrate droplets are <650 nm
- MPPS tends to be in 200-300 nm range
- Viral aerosol challenges may be least rigorous microbial challenge

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Viral aerosol challenge

- Challenge size may be larger than virus depending on drying and size cannot be precisely established
- Viral spike solution is typically prefiltered to remove aggregates (0.2-0.1 µm)
- Higher flow rates may be worst-case since they diminish diffusional interception
- Impinger fluid is analyzed for the test particle with an infectivity assay
- A presence/absence test can be performed on the remaining fluid

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Integrity tests

- Retention challenges should be correlated to an integrity test
- Traditional wetted membrane tests using a low surface tension fluid
  - Bubble Point Test
  - Diffusive/Forward Flow Test
  - Pressure Hold/Decay Test
- Water Intrusion Test (WIT)
- Aerosol Integrity Test

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WIT

- Water Intrusion Test does not involve wetting the membrane with solvent
- The upstream side of the filter is flooded with water, pressurized and allowed to stabilize ~10 minutes
- The flow of water vapor through the membrane is measured over time
- Useful test for new filters, filter must be dry prior to testing

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Aerosol integrity test

- Historically used for detecting failures in HEPA and ULPA grade filters
- Filter is challenged with $10^7/cm^2$ 0.2-0.3 µm aerosol generated from highly refined mineral oil
- A downstream sensor (laser particle counter) detects oil droplets that penetrate the filter
- Can be correlated to aerosol microbial challenge

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When to integrity test

- Before sterilization – right filter, correctly installed
- Post sterilization – also detects if the filter was damaged during sterilization
- Post use – confirms filter remained good throughout the critical process

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Extended use applications

- Parallel filters, use one while other is being tested and prepared for use
- Redundant filters with periodic testing and change-out
- Combination of periodic testing and change-out
- Test once only, after the first sterilization
- Do not test filters and base change-out on historical data (# sterilization cycles or time on line)

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User validation of critical applications

- Generic data correlating retention (bacterial or viral) to the integrity test
- Qualification data for toxicity, durability, compatibility, recommendations for integrity test parameters
- Evaluate retention data applicability to process
  - liquid-rated represents worst case
- Physical integrity test
- Compatibility and service life in use
  - May be demonstrated by integrity testing filter

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Criteria	Filter user	Filter manufacturer
	Device	Disc /Device
Bacterial retention/integrity test relationship data	(E)	(Q)
Integrity test	-	(Q/R/L)
Integrity test method & selection	(E)	(R)
Microbial/viral retention (liquid/aerosol)	(E)	(Q/L)
Compatibility/ service life	(E/V)	(Q/R)
Toxicity testing	-	(Q)
Effects of sterilization method on filter integrity	(E/V)	(Q)

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